IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

MAX WELLS,	§	
	§	
PLAINTIFF,	§	
	§	
vs.	§	CAUSE NO. A-06-CA-126-LY
	§	
SMITHKLINE BEECHAM	§	
CORPORATION,	§	
	§	
DEFENDANT.	§	

MOTION FOR SUMMARY JUDGMENT AS TO PREEMPTION

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Pursuant to Federal Rule of Civil Procedure 56, Defendant SmithKline Beecham Corporation d/b/a GlaxoSmithKline ("GSK") files this Motion for Summary Judgment on grounds of federal preemption under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 *et seq.*) ("FDCA") or, alternatively, under the presumption of adequate warnings under Texas Civil Practice and Remedies Code § 82.007. In support, GSK shows the Court as follows:

INTRODUCTION

Plaintiff Max Wells ("Wells") brought this products liability case against GSK and others, alleging as to GSK that the company failed to properly or adequately warn of potential side effects associated with its prescription medication Requip (ropinirole).[1] Specifically, Dr. Wells claims that Requip caused him to have a "gambling compulsion"[2] and lose $14 million. As explained, Dr. Wells' claims fail as a matter of law for at least two reasons.

First, Dr. Wells' warnings claims are preempted under the FDCA. Although it is not entirely clear what Dr. Wells claims was inadequate in the labeling that GSK has been using, to the extent that he is asking this Court to impose a requirement that is different from what FDA has required, that claim is preempted by federal law. FDA has thoroughly considered the relationship between Requip and compulsive gambling and has concluded that there is insufficient evidence to establish a causal relationship. Further, GSK has used an FDA-approved label for Requip at all times, and that label has contained information about pathological gambling since 2005.[3]

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[1] The trade name is Requip, and the generic name is ropinirole.

[2] First Amended Complaint of Max Wells ("Complaint"), ¶ 14.

[3] A prescription drug label contains a variety of information about safety, including proven side effects, possible associations with medical conditions or disease, and anecdotal reports of adverse events, which may be purely coincidental. FDA divides the labeling into sections in order to more accurately and

In October 2006, GSK revised the Requip label again to broaden the language to include compulsive behaviors and moved it to the PRECAUTIONS section of the label. FDA has recently directed GSK to remove this information from the general PRECAUTIONS section of the Requip label and instead place it in a subsection of the label entitled Information for Patients**.** This is because, according to FDA, the "Precautions/Warnings" section of a prescription product label is reserved for risks that have more definite information regarding causality, which the agency has concluded is lacking in this case. FDA has directed this label change to insure that all drugs in the class of "drugs that increase dopaminergic tone" convey the same message about the possibility of compulsive behaviors—both in terms of the language used and the placement of that language in the prescription labels for this class of products.

By congressional delegation, labeling decisions like these are within FDA's sole and exclusive province; the agency serves as the final arbiter for all information necessary and appropriate in a prescription label. FDA has concluded that there is a significant risk to national health when prescription drug warnings "include theoretical hazards not well-grounded in scientific evidence, [which] can cause meaningful risk information to 'lose its significance.'"[4] Put another way, "overwarning" has the potential to discourage safe and effective use of approved products or to encourage inappropriate use and undermine the objectives of federal pharmaceutical law.[5]

As a result, FDA has definitively stated its position that failure to warn claims like Dr. Wells'—that would effectively require warnings over and above what FDA concluded were

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consistently communicate safety information. *See, e.g.*, Department of Health and Human Services, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products* (21 C.F.R. parts 201, 314, and 601), 71 Fed. Reg. 3922, 3924 (Jan. 24, 2006).

[4] *See* 71 Fed. Reg. at 3935-36.

[5] *Id.* at 3936.

appropriate—are preempted by FDA's comprehensive "regulation of prescription drug labeling."[6] This statement by the agency—which is "the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective"[7]—is dispositive on the question of implicit intent to pre-empt under the circumstances presented. FDA has concluded that there is insufficient scientific evidence of a causal connection between Requip and compulsive gambling and has required GSK to remove language from the Precautions/Warnings section regarding an association like the one Dr. Wells asserts. His judicial attempt to second-guess FDA's decision is preempted by federal law.

Second, the claim is barred under Texas law. Since September 2003, Texas has barred failure-to-warn claims against pharmaceutical companies—like those Dr. Wells has asserted here—if the prescription drug is accompanied by FDA approved warnings: A manufacturer is not liable if "the warnings . . . that accompanied the product . . . were those approved by the United States Food and Drug Administration . . . ."[8] There is no question that the warnings accompanying Requip have at all times been approved by FDA. While § 82.007 includes several narrow exceptions, Dr. Wells has not alleged that any of the exceptions apply. Consequently, even if the Court finds that Dr. Wells' warning claims are not preempted under federal law, GSK is independently entitled to summary judgment as a matter of Texas law.

Background

Dr. Wells alleges that he began taking Requip to treat his Parkinson's disease in the fall of 2004. First Amended Complaint of Max Wells ("Complaint"), at ¶ 13; *see also* Deposition of

[6] *Id.* at 3935–36.

[7] *Id.* at 3934.

[8] TEX. CIV. PRAC. & REM. CODE ANN. § 82.007 (Vernon 2005).

Max Michael Wells at Volume 4, 79:23-80:3 ("Wells Depo.") (Exhibit A).[9] Parkinson's is a progressive, neurodegenerative, disorder that occurs when certain dopamine-producing brain cells begin to die and the amount of dopamine produced decreases, resulting in a loss of coordinated movement and initiated movement, among other symptoms. *See* Deposition of Sara A. Westgate, M.D., Ph.D at 270:4-20; 273:8-274:5 ("Westgate Depo.") (Exhibit B). Requip is a dopamine agonist, which is "essentially a dopamine mimicker" that acts like dopamine in the brain. *Id.* at. 275:4-13. It has been effective in a number of Parkinson's patients, including Dr. Wells, in alleviating Parkinson's disease symptoms. *Id.* at 259:10-13; 261:11-262:12.

Prior to the time he took Requip, Dr. Wells had been prescribed Mirapex (pramipexole), another prescription medication for the treatment of Parkinson's disease. However, Dr. Wells—who is himself a physician—read an article about Mirapex suggesting a possible association with pathological gambling,[10] and brought it to the attention of his treating doctor. *Plaintiff's Response to Defendant SmithKline Beecham Corporation d/b/a GlaxoSmithKline's First Interrogatories* ("Plaintiffs' Interrogatory Response"), at No. 12 (Exhibit W); *see also* Wells Depo. at Vol. 4, 47:5-50:23, 51:6-52:1. In November 2004, Dr. Wells indicated that his physician switched him from Mirapex to Requip due to his belief that Mirapex contributed to his

[9] The summary judgment exhibits supporting this motion and GSK's contemporaneously filed *Motion for Summary Judgment on Causation* and *Motion to Preclude Proposed Expert Testimony Pursuant to Federal Rules of Evidence 702 and 703 and for Summary Judgment*, are contained in a separately, but contemporaneously, filed Documentary Evidence Notebook. Subsequent references to the five-volume Wells' Depo. will be abbreviated to list the Volume and page and line numbers as follows: "Wells Depo. Vol. 4, 79:23-80:3."

[10] Driver-Dunckley et al, *Pathological gambling associated with dopamine agonist therapy in Parkinson's disease*, NEUROLOGY (2003). None of the 421 patients taking Requip in this study developed compulsive gambling. Of the nine patients taking other Parkinson's drugs who did develop compulsive gambling—eight of whom were taking Mirapex—***six patients had a "sustained resolution of symptoms after switching to [Requip]***." *Id.* (emphasis added). In other words, their gambling stopped after they switched to Requip.

compulsive gambling. Complaint ¶ 13; Plaintiffs' Interrogatory Response, at Nos. 4, 11; Wells Depo. Vol. 4, 80:4-7; Westgate Depo. at 238:18-22.

Requip has been approved by FDA for the treatment of both idiopathic Parkinson's disease and Restless Legs Syndrome ("RLS"). *See, e.g.*, Deposition of Leslie Rogers, M.D. ("Rogers Depo.") (Exhibit C) at 101:24-102:2; 168:10-25 & Exhibit 218.[11] As part of both approval processes, and in keeping with post-marketing requirements, GSK has shared volumes of data with FDA. *Id.* at 159:5-19; 163:13-164:25. Requip has always been distributed with labels that have been approved by FDA, Rogers Depo. at 174:10-13,[12] and Dr. Wells does not allege otherwise. *See* Complaint ¶¶ 9-19. An overview of the regulatory approval process is provided below to demonstrate the primacy of FDA's role in prescription product labeling.

I. Labeling is A Crucial Component of FDA's Oversight of Prescription Drugs

FDA's statutory mandate is to "protect the public health by ensuring that . . . drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B). To carry out that mandate, FDA employs a rigorous, detailed, and highly regulated, multi-step approval process. Over the course of the lengthy approval process,[13] FDA reviews voluminous information describing the drug's chemical composition; the mechanism by which the drug works in the body; the results of laboratory and animal tests relating to the pharmacological and toxicological properties of the potential drug; the design and results of clinical trials of the drug in humans; safety and efficacy

[11] References to numerical exhibits are to deposition exhibits from Dr. Rogers Deposition. The referenced deposition exhibits are included in Exhibit C.

[12] As explained below at part II, GSK made several label changes through the FDA's CBE process, which does not require ***prior*** approval, but FDA must ultimately approve of the label change. 21 C.F.R. § 314.70(c)(7); Rogers Depo. at 172:16-173:9. FDA never disapproved of any of these label changes, nor did it conclude that they were misleading in any way or rendered the product misbranded. Rogers Depo. at 173:23-175:23; 176:13-25; 179:15-180:20.

[13] In fact, Requip was approved for use in Parkinson's patients nine years after GSK submitted the initial Investigational New Drug Application to FDA. *See, e.g.*, Rogers Depo. Exhibits 214 (dtd. June 10, 1988) & 218 (dtd. Sept. 19, 1997).

information relating to the company's proposed indication(s) for the drug; as well as the proposed labeling. *See generally* 21 U.S.C. § 355.

FDA's duty to ensure the safety and efficacy of prescription drugs is inextricably linked to its duty to regulate drug labeling. Department of Health and Human Services, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products* (21 C.F.R. parts 201, 314, and 601), 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) ("[T]he FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective ***and*** that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading." (emphasis added)). The agency "carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use." *Id.* Consequently, FDA will not approve a drug if its labeling is "false or misleading in any particular." 21 U.S.C. § 352(a), (f) & (j).

FDA has explained that its role in approving drugs and their labeling involves weighing both technical and public policy considerations. Drug labeling is at the heart of maintaining that delicate balance. In FDA's own words, the agency:

> makes approval decisions based not on abstract estimation of [a prescription product's] safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended or suggested in the labeling. FDA considers not only complex clinical issues related to the use of the product in study populations, but also important and practical public health issues pertaining to the use of the product in day-to-day clinical practice, such as the nature of the disease or condition for which the product will be indicated, and the need for risk management measures to help assure in clinical practice that the product maintains its favorable benefit-risk balance. ***The centerpiece of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and***

> ***effectively. FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help insure safe and effective use***.

71 Fed. Reg. at 3934 (citing 21 U.S.C. § 355(d)) (emphasis added). FDA's "formal, authoritative conclusions" expressed in a drug's labeling are not merely minimum safety standards. *Id.* at 3935. "In fact, FDA interprets the [FDCA] to establish both a 'floor' and a 'ceiling,' such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading." *Id*. Significantly, a drug manufacturer cannot include in its labeling "theoretical hazards not well-grounded in scientific evidence." *Id.*

FDA's duty to protect the public health does not end with a drug's approval. The agency is required to "promptly and efficiently review[] clinical research and tak[e] appropriate action on the marketing of regulated products in a timely manner." 21 U.S.C. § 393(b)(1). Thus, after the drug has been approved for marketing, both the company and FDA monitor its safety and continue to review the risks and benefits associated with the drug. 21 C.F.R. § 314.80; *see also* Rogers Depo. at 169:24-171:9. The company must periodically submit any new information to FDA regarding the continued safety, efficacy and/or labeling of the drug. 21 U.S.C. § 355(k) (describing a manufacturer's post-marketing reporting and record-keeping requirements); Rogers Depo. at 169:24-171:9. Likewise, FDA's duty to regulate prescription drug labeling continues long after a drug's initial label is approved, and the agency "continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate." 71 Fed. Reg. at 3934.

Typically, a new drug continues to undergo evaluations in clinical trials following its initial marketing approval. *E.g.*, Rogers Depo. at 10:25-12:3. Data from completed clinical

trials are compiled, analyzed, and submitted to FDA in accordance with federal regulations. *Id.* at 13:7-22; 26:17-27:7. Both the drug manufacturer and FDA also monitor and analyze spontaneous adverse event reports, which are reports of adverse events that occurred in patients taking a medication, as well as information "that might affect the safety, effectiveness, or labeling of the drug product." 21 C.F.R. §§ 314.80(c) & 314.81(b)(2)(i); Rogers Depo. at 14:8-15:24; 169:24-171:9. Physicians, pharmacists, nurses, other health care professionals, lay persons, and even lawyers representing claimants can submit adverse event reports, either to the manufacturer or to FDA. Rogers Depo. at 14:12-17; 15:17-24; 23:22-25:12. If the adverse event reports are sent to the manufacturer, the manufacturer sends the information to FDA. *Id.* at 11:13-12:3. The company also reviews scientific and medical literature—such as clinical and preclinical reports, summaries, case histories, and articles published in journals—for information about safety and reports it to FDA in accordance with federal regulations. *Id.* at 33:13-34:20. Both FDA and the company regularly analyze this data to determine if changes should be made to the drug's label, such as changes to the adverse events, warnings, precautions, or contraindications sections of the label. *Id*. at 55:23-57:2; 87:8-12; 91:17-92:4. If FDA were to conclude that the drug was no longer safe or effective under the conditions of use specified in its labeling, the agency would withdraw its approval. 21 U.S.C. § 355(e).

With a few minor exceptions that are not relevant here, post-approval labeling changes must be submitted to FDA in a supplemental application that fully explains the basis for the change. 21 C.F.R. § 314.70; Rogers Depo. at 168:15-169:23. Most supplements require FDA approval before the change is made, but if a drug manufacturer wishes to add or strengthen a warning, it may submit a "changes being effected" ("CBE") supplement, which allows it to make the change "prior to FDA approval, but after FDA notification." 71 Fed. Reg. at 3934; 21 C.F.R.

§ 314.70(c)(6)(iii); Rogers Depo. at 171:12-172:15. The CBE changes only the timing of FDA's approval because the agency may later deny approval of the change and take enforcement actions, including declaring the product misbranded, seizing the product, and/or order the company to cease and desist distribution. 21 C.F.R. § 314.70(c)(7); Rogers Depo. at 172:19-173:9. According to FDA, "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act." 71 Fed. Reg. at 3934.

II. Requip's Labeling Is FDA-Approved

Requip was approved by FDA for use in patients with idiopathic Parkinson's disease in 1997 and for use in patients with Restless Leg Syndrome in 2005. *See, e.g.*, Rogers Depo. at 101:24-102:2; 168:10-25 & Exhibit 218. Prior to both approvals, and in keeping with federal regulations, GSK performed extensive clinical studies to test the safety and efficacy of the drug. *Id.* at 162:2-16. FDA approved the design of the studies, reviewed the results of the clinical data, and specifically approved Requip's labeling. *Id.* at 159:3-161:23; 163:19-164:3; 168:10-169:18 As noted, pursuant to its post-marketing obligations, GSK has shared information regarding Requip with FDA since the time that the drug was first approved. *Id.* at 170:7-171:9.

Requip has always been distributed with labels that have been approved by FDA, Rogers Depo. at 174:10-13, and Dr. Wells does not allege otherwise. *See* Complaint ¶ 9–19. Instead, Dr. Wells alleges that by "mid-2005," GSK should have "reasonably foresee[n] that Parkinson's patients using Requip could develop an irresistible gambling compulsion as a side effect of taking the drug." Complaint ¶ 18. According to Dr. Wells, the "association [between dopamine agonists and compulsive gambling] was widely known in the pharmaceutical community and was included in warnings for Mirapex, another dopamine agonist used in treating Parkinson's Disease, significantly prior to its appearance in warnings written for Requip." *See* Plaintiffs' Interrogatory Response, at No. 13.

A. In 2005, GSK Submits a Label Change to Add Information About Compulsive Gambling

GSK has been monitoring all adverse event reports for Requip, including pathological gambling, and it was not until the summer of 2005 that GSK concluded there was some information that supported a label change. Rogers Depo. at 83:23-85:04;105:2-24. Although there was still no reason to suspect any causal relationship between Requip and compulsive gambling—indeed, even today there is insufficient evidence to establish one[14]—GSK amended its label for Requip in July 2005 under FDA's CBE[15] regulations to include the following language under "**ADVERSE REACTIONS**":

> **Post-marketing Reports:** Pathological (compulsive) gambling has been reported in a small number of patients, primarily with Parkinson's disease, treated with dopaminergic agents, including Requip. It is not possible to `determine the causal relationships between these events and Requip. In some cases other factors were present such as a history of problem gambling or concurrent dopaminergic treatment.

Rogers Depo. at 173:10-174:5; 184:24-185:5 & Exhibit 219 (Prescribing Information for Requip® (ropinirole hydrochloride) RQ:L12). This July 22, 2005, CBE contained the effective language for pathological gambling until the fall of 2006. Rogers Depo. at 175:17-176:2. Dr. Wells asserts that he did not read the Requip package insert until January of 2006. *See* Plaintiff's Interrogatory Response, at No. 9.

B. GSK Submits Another CBE for the Requip Label

GSK continued to monitor scientific literature and adverse event reports for Requip. Rogers Depo. at 113:5-114:7. The company undertook a full evaluation of

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[14] *See Motion for Summary Judgment as to Causation*, filed contemporaneously and incorporated by reference.

[15] As explained above at part I, a manufacturer can in certain instances change its label without prior approval by FDA, but it must notify FDA of the change through a "changes being effected" supplement, and FDA must ultimately approve the label change.

impulsive/compulsive behaviors, including pathological gambling and hypersexuality, in patients receiving ropinirole treatment. *See* Exhibit V at RQNDAA0540607. As part of that process, GSK reviewed its clinical safety database, clinical trials database, and published information in the medical literature for reports of impulse control symptoms, including compulsive behaviors. *Id.* at RQNDAA0540609; *see also* Rogers Depo. at 113:25-114:4; 176:6-25 & Exhibit 220. At the end of this evaluation, GSK concluded that it would be appropriate to update the Requip label to alert prescribers to certain adverse events. *Id.* at RQNDAA0540628; *see also* Rogers Depo. at 114:5-7. As a result, GSK submitted a CBE for Requip to FDA on October 3, 2006. Rogers Depo. at 176:12-177:15 & Exhibit 220. The CBE confirmed that GSK had revised its labeling for Requip to add a new subheading under "PRECAUTIONS":

> ***Impulse Control Symptoms Including Compulsive Behaviors:*** Impulse control symptoms, including compulsive behaviors such as pathological gambling and hypersexuality, have been reported in patients treated with dopaminergic agents, including ropinirole. As described in the literature, such behaviors have been reported principally in Parkinson's disease patients treated with dopaminergic agents, especially at higher doses, and were generally reversible upon dose reduction or treatment discontinuation. In some cases with ropinirole, other factors were present such as a history of compulsive behaviors or concurrent dopaminergic treatment.

Rogers Depo. 176:6-25 & Exhibit 220 at RQNDAA0540576 (Prescribing Information for Requip® (ropinirole hydrochloride) RQ:L15).

> Under "Information for Patients," the following was added:
>
> Patients should be informed that some patients taking ropinirole have shown urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble or increased sexual urges and/or behaviors. If patients or their family notice that they are developing any unusual behaviors, they should talk to their doctor.

Id. Exhibit 220 at RQNDAA0540577.

The following language also appeared under "**ADVERSE REACTIONS: Postmarketing Reports**":

> ***Psychiatric Disorders:*** Impulse control symptoms, pathological gambling, increased libido including hypersexuality.

Id. Exhibit 220 at RQNDAA054091.

On October 6, 2006, after undertaking its own review of the literature and adverse event reports as to Requip and other dopamine agonists, FDA sent a letter to GSK requesting that GSK add information about compulsive behavior to its Requip label under Information for Patients. Rogers Depo. at 177:1-19 & Exhibit 221. The letter does not mention GSK's October 3, 2006, CBE, and the two letters appear to have crossed in the mail. *Id.* at 123:19-124:3; 177:16-19. In its October 6 letter, the FDA specifically indicated that it believed the available information did not support a finding of a cause and effect relationship between Requip and intense urges; however, it also stated that it believed that patients should be informed about the potential for experiencing intense urges when using these medications. *Id.* Exhibit 221 at 1. FDA also recognized that additional research was necessary and requested GSK to provide results of any testing and information about planned future studies of a possible association. *Id.*

The parties held a conference to discuss, and GSK sent FDA a follow-up letter on November 11, 2006, reciting the points on which the parties had agreed. Rogers Depo. at 179:3-25; 180:21-183:6 & Exhibit 222. GSK was informed that the parties were in agreement that GSK's October 3, 2006 submission qualified as a CBE Supplement, that it should not "cease and desist" on the current labeling as modified by the CBE, and that further review was needed. Rogers Depo. at 179:15-180:17.

C. FDA Concludes That Another Labeling Change Is Necessary to Deemphasize the Compulsive Behavior Risk

In November 2007, FDA advised GSK that it had concluded that the compulsive behavior information should be relocated to a different part of the Requip label and that the agency would provide the required language. Rogers Depo. at 180:21-183:1 & Exhibits 206 & 222. FDA directed GSK to remove the compulsive behavior information from the PRECAUTIONS and ADVERSE REACTIONS/Post-Marketing sections of the label and that FDA's language[16] be added to the Information for Patients section. *Id.* Exhibit 222 at GSKMW0032896. GSK was informed that the change represents FDA's view that this risk information had been overly emphasized in light of the available evidence of causality. *Id.* Exhibit 222 at GSKMW0032896; *see id.* at 181:25-182:18. According to FDA, the information regarding compulsive behaviors came mostly from postmarketing reports, which is difficult to interpret in terms of causality. *Id.*; *see also id.* at 181:25-182:3. FDA further explained to GSK that, without definite information regarding causality, FDA recommends that such information should be placed in the Information for Patients subsection of the Precautions section of the label. *Id.; see also id.* at 182:4-10. The agency also indicated that the language it prescribed was

[16] Specifically, FDA requested that the Information for Patients subsection of "PRECAUTIONS" be revised to add:

> There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone, that are generally used for the treatment of Parkinson's disease or Restless Legs Syndrome, including Requip. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with Requip. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking Requip. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Requip.

Rogers Depo. Exhibit 206 at GSKMW0064503. This is virtually the same language that was proposed by FDA in October 2006. *See id.* Exhibit 205 at GSKMW0061045.

"class labeling," meaning that it is to be used in all labels for "all drugs that increase dopaminergic tone." *Id; see also id.* at 182:19-183:1. FDA has since sent a draft label with the revised language that GSK is required to use. *Id.* at 126:13-127:15; Exhibit 206 at GSKMW0064504.33

FDA has thus carefully calibrated the risk information that it believes should be communicated to health care providers as to the entire class of these products, including Requip. FDA's decision constitutes its "formal, authoritative conclusions" expressed in the labeling," which, as noted previously, "are not merely minimum safety standards . . . [because] a drug manufacturer cannot include in its labeling "theoretical hazards not well-grounded in scientific evidence." 71 Fed. Reg. at 3934-35. Dr. Wells' challenge to the agency's complex and comprehensive labeling decision should be addressed to FDA—"the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective"[17]—not a lay jury.

ARGUMENT AND AUTHORITIES

I. Dr. Wells' Failure to Warn Claims Are Preempted by Federal Law

A. Conflicts Preemption Applies When State Laws Frustrate the Purpose of Federal Laws

Under the Supremacy Clause of the U. S. Constitution, U.S. CONST Art. VI, federal law overrides state law that interferes with, or is contrary to, federal law in three instances: (i) when Congress expressly preempts state law (express preemption); (ii) when Congressional intent to preempt can be inferred from the existence of a sufficiently comprehensive federal regulatory scheme (field preemption—implied); or (iii) when state law actually conflicts with federal law or its purposes (conflicts preemption—implied). *Colacicco v. Apotex, Inc.*, 521 F.3d 253, 261 (3d Cir. 2008) (quoting *Hillsborough County v. Automated Med. Labs, Inc.*, 471 U.S. 707, 712

[17] 71 Fed. Reg. at 3934.

(1985)). "[T]he purpose of Congress is the ultimate touchstone" in every preemption case. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 494 (1996) (internal quotations and citations omitted).

Conflicts preemption, which is the type of preemption at issue here,[18] occurs either "when compliance with both federal and state regulations is a physical impossibility, . . . or when state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hillsborough County*, 471 U.S. at 713 (quoting *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142–43 (1963) and *Hines v. Davidowitz*, 312 U.S. 52, 66–67 (1941) (internal quotation marks omitted)); *see also Geier v. Am. Honda Motor Co., Inc.*, 529 U.S. 861, 873 (2000) (declaring that conflicts preemption applies anytime state law stands as an obstacle to federal law, "whether that 'obstacle' goes by the name of 'conflicting; contrary to; . . . repugnance; difference; irreconcilability; inconsistency; violation; curtailment; . . . interference,' or the like") (citing *Hines*, 312 U.S. at 67). Federal regulations "have no less pre-emptive effect than federal statutes." *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982); *Hillsborough County*, 471 U.S. at 713 ("We have held repeatedly that state laws can be pre-empted by federal regulations as well as by federal statutes.").

Dr. Wells' claim that GSK failed to provide adequate warnings that Requip could "cause its users to develop an irresistible impulse to gamble," Complaint ¶ 9, is a request that this Court find GSK's FDA-approved label inadequate. To do as Dr. Wells asks and hold GSK liable for using a label that was approved by FDA would frustrate the objectives of federal prescription

[18] The FDCA does not contain a general express preemption provision, but it is clear that Congress did not intend to preclude conflicts preemption—*i.e.*, where state law claims conflict with FDA determinations. *See* 21 U.S.C. § 202 (referred to in historical note to 21 U.S.C.A. § 321 (West 1999) ("Nothing in the amendments made by this Act to the Federal Food Drug & Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments ***unless there is a direct and positive conflict*** between such amendments and such provision of State law.") (emphasis added); *see also Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 869 (2000) (savings clauses do "*not* bar the ordinary working of conflict pre-emption principles") (emphasis in original).

drug labeling requirements. Consequently, and as explained in more detail below, Dr. Wells' claims are preempted by federal law.[19]

B. FDA Has Definitively Stated That Claims Like Dr. Wells' Are Preempted

1. FDA's Position on Preemption Is Definitive and Entitled to Deference

As noted above, in the preamble to its recent labeling rule, FDA addressed the role of preemption in prescription drug labeling. 71 Fed. Reg. at 3933–36. FDA explained that it had previously asked the Department of Justice to file amicus briefs in tort suits throughout the country to express the agency's official position that FDA labeling decisions should preempt contrary state law. *Id.* at 3934. Considering it to be "useful to set forth in some detail the arguments made in those amicus briefs," FDA stated that the preamble discussion "represents the government's long standing views on preemption, with a particular emphasis on how that doctrine applies to State laws that would require labeling that conflicts with or is contrary to FDA-approved labeling." *Id.*

That longstanding view is that "under existing preemption principles, FDA approval of [prescription drug] labeling . . . preempts conflicting or contrary state law." *Id.* Specifically, "[s]tate laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated." *Id.* at 3935.

[19] Although there is a general "assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress," *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947), "this historical preference does not foreclose the possibility of preemption, where applicable." *Pa. Employees Ben. Trust Fund v. Zeneca, Inc.*, 499 F.3d 239 n.11 (3d Cir. 2007); *see also Felder v. Casey*, 487 U.S. 131, 138 (1988); *Colacicco v. Apotex, Inc.*, 521 F.3d 253, 265 (3d Cir. 2008) (noting a tension between a presumption against preemption and implied conflicts preemption, "which analyzes preemption in the absence of any explicit intent"). Further, regulation of drug labeling has been a province of the federal government for over a hundred years, and so, the police powers of the States can hardly be said to justify a presumption against preemption. *See, e.g.*, *United States v. Locke*, 529 U.S. 89, 108 (2000) (noting that there is no presumption against federal preemption in areas of significant federal presence).

Based upon its extensive and lengthy experience with these issues, FDA has concluded that claims like Plaintiffs'—seeking to hold a pharmaceutical company liable for failing to include warnings that FDA has rejected or "are not supported by evidence . . . reflect[ing] [k]nown hazards and not theoretical possibilities"—should be preempted. 71 Fed. Reg. at 3936. FDA's statements on the preemptive effect of its regulatory authority are entitled to deference.[20] *See Riegel v. Medtronic, Inc.*, 552 U.S. ___, 128 S. Ct. 999, 1009 (2008) (suggesting that deference under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944), would be accorded to agency interpretation of preemptive effect if express preemption statute were ambiguous).

Even before FDA's express preemption statement, the Fifth Circuit has considered the argument that "state law would impermissibly conflict with federal law if it required a warning different from that approved and required by FDA" to be "compelling." *Hurley v. Lederle Labs., Div. of Am. Cyanamid Co.*, 863 F.2d 1173, 1176–79 (5th Cir. 1988). In *Hurley*, the Fifth Circuit addressed whether a vaccine products liability claim was preempted by federal law. "Thus," the court wrote, "assuming that FDA has processed all the relevant and available information in arriving at the prescribed warning, ***its decision as to the proper wording must preempt by implication that of a state***." *Id.* at 1179 (emphasis added).[21]

Here, deference to FDA's position is particularly appropriate because of the technical and scientific nature of its regulatory authority. *See Geier*, 529 U.S. at 883. In *Geier*, the Supreme

[20] The Supreme Court has specifically stated that an agency's preemptive intent can be addressed in a preamble. *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 718 (1985).

[21] Because a fact issue remained as to whether FDA had in fact been provided all necessary information, the court remanded to the trial court, directing that "the only question that can be presented to the jury consistent with the federal regulatory scheme is whether the manufacturer withheld, either at the time FDA decided the content of the warning, or since then, information that would have changed FDA's decision." *Hurley v. Lederle Labs.*, 863 F.2d 1173, 1179–80 (5th Cir. 1988).

Court placed weight on the Department of Transportation's conclusion that a state tort claim would conflict with the agency's objectives:

> Congress has delegated to DOT authority to implement the statute; ***the subject matter is technical***; and the relevant history and background are complex and extensive. ***The agency is likely to have a thorough understanding of its own regulation and its objectives and is "uniquely qualified" to comprehend the likely impact of state requirements.***

Id. (emphases added); *Henley v. FDA*, 77 F.3d 616, 620 (2d Cir. 1996) ("FDA's determination of what labeling best reflects current scientific information regarding the risks and benefits" of a prescription product "involves a high degree of expert scientific analysis." (internal quotations and citation omitted)); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of FDA's expertise and merit deference from us."); *Hurley*, 863 F.2d at 1179 ("A state law determination on this issue should not be interjected to overrule the decision of FDA. . . . FDA extensively regulates the contents and wording of these product inserts.").

The Third Circuit has held that, where the FDA has specifically rejected the need for a warning claimed by the plaintiff to be required by state law, an inadequate-warnings claim based upon the perceived inadequacy of the warning is preempted. *Colacicco*, 521 F.3d at 271; *see also Pa. Employees Benefit Trust Fund v. Zeneca, Inc.*, 499 F.3d 239, 243, 251 (3d Cir. 2007) ("[T]he purpose of protecting prescription drug users in the FDCA would be frustrated if states were allowed . . . to permit[] plaintiffs to question the veracity of statements approved by FDA."). In *Colacicco*, the plaintiffs asserted that the manufacturers of certain antidepressants, known as selective serotonin reuptake inhibitors ("SSRIs"), should have included warnings about potential suicide risks that FDA had publicly and repeatedly indicated were "without scientific basis and would therefore be false and misleading." *Colacicco*, 521 F.3d at 269. The court found that the plaintiffs' claims were therefore preempted by FDA's determination,

notwithstanding the fact that FDA had not specifically rejected any proposed labeling change. *Id.* at 272 ("We agree that a court could more easily determine the preemption issue if the FDA had formally rejected such a CBE supplement, but we cannot compel the defendant companies to suggest a CBE supplement that they believe is unnecessary.").

Notably, the United States Supreme Court has granted certiorari review in a case coming to a contrary conclusion. In *Levine v. Wyeth*, 944 A.2d 179, 184 (Vt. 2006), the Vermont Supreme Court held the preemption preamble to FDA's new labeling rule not to preempt state tort claims. In doing so, the Vermont court concluded that the defendant could have added to its warning without prior FDA approval and because "federal labeling requirements create a floor, not a ceiling, for state regulation." *Id.* In an amicus brief, the Solicitor General asserted that:

> Respondents' claims are preempted because they challenge labeling that FDA approved after being informed of the relevant risk.
>
> * * *
>
> Because FDA's approval strikes a balance between competing considerations, state laws that strike a different balance conflict with FDA's determinations and are impliedly preempted.

Brief for the United States as Amicus Curiae, *Wyeth v. Levine*, No. 06-1249, 2008 WL 230890 (June 2, 2008) at 7-8. As was the case in *Colacicco* and *Levine*, FDA has thoroughly studied the scientific developments as to a claimed association between Requip and compulsive gambling, has repeatedly concluded that there is no causal connection between the two, and has directed changes to GSK's approved label for Requip (as well as other drugs in the same class) in keeping with FDA's conclusions. FDA has prescribed the warning information down to the precise language and placement on the Requip label. Dr. Wells' attempt to "strike a different balance" is thus preempted.

2. Dr. Wells' Warnings Challenges Are Preempted

Of course, conflicts preemption only bars state tort claims that actually conflict with federal law or its purposes, and the "FDA's regulation of drug labeling will not preempt all State law actions." 71 Fed. Reg. at 3936. Specifically, "certain State law requirements that ***parallel*** FDA requirements may not be preempted." *Id.* (emphasis added). Dr. Wells' claims, however, do not parallel FDA requirements—if they did, Dr. Wells' recovery would have been doomed from the outset because GSK's labels have always complied with FDA's requirements. Instead, Dr. Wells seeks to hold GSK liable for using a label that was approved by FDA at the time Dr. Wells claims the label was deficient. Specifically, Dr. Wells' Complaint makes two allegations: (1) GSK ***failed to warn*** that Requip can ***cause*** compulsive gambling, *see* Complaint ¶¶ 9, 18; and (2) GSK "***minimized*** the ***association*** between Requip and the possibility of a side effect of creating a gambling compulsion." Complaint ¶ 18 (emphasis added). FDA has specifically indicated that both types of claims are preempted under the circumstances presented here.

In the preamble, FDA provided several specific categories of claims that, consistent with "existing preemption principles," would impermissibly conflict with federal law. 71 Fed. Reg. at 3935–36. Dr. Wells' claims fall into at least two of these categories:

> (1) Claims that a drug sponsor breached an obligation to warn by failing to put in Highlights or otherwise emphasize any information the substance of which appears anywhere in the labeling;
>
> . . .
>
> (3) claims that a sponsor breached an obligation to warn by failing to include contraindications or warnings that are not supported by evidence that meets the standards set forth in this rule, including § 201.57(c)(5) (requiring that contraindications reflect "[k]nown hazards and not theoretical possibilities") and (c)(7) [(requiring that adverse reactions reflect "only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event")]

Id. at 3936. Dr. Wells' claim that GSK minimized an association between Requip and compulsive gambling would fall under the first category, and both claims would be barred under the second.

a. Failure to include warnings not supported by evidence

As explained above in the Background section of this motion, GSK amended the Requip label several times in its effort to communicate accurate information to the prescribers—at all times with the express or implicit approval of FDA. *See Dowhal v. SmithKline Beecham Consumer Health Care*, 32 Cal. 4th 910, 919 (Cal. 2004) ("Once an application has been approved, any change in the labeling requires a supplement to the application and approval by the FDA, either before or after the change."). After thorough consideration of the available science and practical information as to the entire class of drugs that increase dopaminergic tone, FDA has determined precisely what language should be used to communicate information about compulsive behaviors and precisely where that language should be located on the labeling. In doing so, FDA has made clear that a causation warning would not be appropriate. *See, e.g.*, Rogers Depo. at 181:25-182:3 & Exhibit 222 at GSKMW0032896. Dr. Wells' argument that a causation warning was required in July of 2005 when FDA has continuously concluded—to this day and with the benefit of even more scientific information—that there is no proof of a causative relationship must therefore fail as a matter of law. *See* 71 Fed. Reg. 3935 ("State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public—the central role of FDA . . ."); *see also Sykes v. GlaxoSmithKline*, 484 F. Supp. 2d 289, 310 (E.D. Pa. 2007) ("Although this statement by the FDA was issued after Wesley received his vaccines, it is reasonable for this court to conclude that the FDA would have reached the same conclusion in 1996, when less

information was available and fewer studies existed discussing a connection between thimerosal and neurological injury."). As a result, Dr. Wells' warning claims are preempted by federal law as impermissibly conflicting with FDA's labeling determinations.

b. Failure to emphasize information that otherwise appears in the labeling

Dr. Wells' claim that GSK "minimized the association between Requip and the possibility of the side effect of creating a gambling compulsion," *see* Complaint ¶ 18, is also preempted because it seeks to impose liability for GSK's alleged failure to "emphasize any information" that appears elsewhere in the labeling. *See* 71 Fed. Reg. 3936. Although Dr. Wells has been asked in interrogatories to detail precisely what he claims is lacking from the Requip label, he has simply stated that GSK failed to adequately warn Plaintiff or Plaintiff's physician of the association between dopamine agonists and compulsive behavior. Plaintiffs' Interrogatory Response at No. 13.[22] Whether Dr. Wells' dissatisfaction with Requip's warning arises from (a) the particular placement of the warning within the label or (b) the fact that the warning also truthfully stated it was "not possible to determine the causal relationships between these events and Requip" and that "[i]n some cases other factors were present such as a history of problem gambling or concurrent dopaminergic treatment," it does not change the fact that FDA has decided exactly what language should be communicated and where it belongs in the Requip label. *See id.*

Preemption of claims that a drug manufacturer failed to emphasize information, when that information actually appears somewhere in the labeling, arises from FDA's complicated and

[22] Dr. Wells says further that "Defendant had specific information regarding an association between Requip and compulsive behavior, including compulsive gambling and failed to include ***any*** warning regarding such association in its product insert, advertisements, or materials provided to physicians." Plaintiffs' Interrogatory Response at No. 13 (emphasis added). It is not at all clear what he means by this contention, considering that the labels in use since 2005 informed prescribers of a possible association between the two.

nuanced risk-benefit analysis that is reflected in a prescription drug's labeling. Emphasizing risks when such emphasis is not scientifically substantiated is essentially a form of overwarning that "can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use." 71 Fed. Reg. at 3935. There is simply no distinction between Dr. Wells' argument that GSK ***minimized*** the association between Requip and gambling and an allegation that GSK ***failed to emphasize*** the association. FDA's most recent directive as to the label demonstrates the importance to FDA of placement of information within the label. FDA has engaged in a careful weighing of the risks and benefits in prescribing the required language and its placement in the label; it is up to FDA—not Dr. Wells or a lay jury—to determine the proper measure of emphasis to place on a particular type of warning, and Dr. Wells' claims are preempted for this reason as well.

II. Under Texas Law, GSK is Entitled to a Presumption of Adequate Warnings

Even if this Court finds that Dr. Wells' claims are not federally preempted, the Texas Legislature has determined that claims like his cannot stand. Under Texas law, an FDA-approved warning on a pharmaceutical product is presumed to be adequate unless the Dr. Wells can satisfy certain very narrow exceptions. TEX. CIV. PRAC. & REM. CODE ANN. § 82.007. The statute provides:

> (a) In a products liability action alleging that an injury was caused by a failure to provide adequate warnings or information with regard to a pharmaceutical product, there is a rebuttable presumption that the defendant or defendants, including a health care provider, manufacturer, distributor, and prescriber, are not liable with respect to the allegations involving failure to provide adequate warnings or information if:
>
> (1) the warnings or information that accompanied the product in its distribution were those approved by the United States Food and Drug Administration for a product approved under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. Section 301 et seq.), as amended, or Section 351, Public Health Service Act (42 U.S.C. Section 262), as amended.

TEX. CIV. PRAC. & REM. CODE § 82.007(a).

The Texas Legislature enacted this provision to ensure that state courts do not second guess the extensive FDA review process. The Legislature discussed at length the rationale behind this statute. *See, e.g.*, Debate on House Bill 4 on the Floor of the House of Representatives, 78th Leg., R.S. 74-75 (March 27, 2003) ("I can tell you that the intent of this section is to say this: if a pharmaceutical product has gone through the rigorous—as the Supreme Court has held—the rigorous review and approval process, and that approval process established a certain set of warnings that need be given with that product, and if a manufacturer or a retailer uses that exact warning that was approved through that rigorous process, then they cannot be held liable for the—for a marketing defects for failure to give the proper warning.").

Thus, the statute was based on the well established and exclusive role of FDA with regard to drug labeling. Here, it is undisputed that all of the warnings accompanying Requip were approved by FDA following FDA's rigorous process. *See* Background part II. As a result, and as a matter of law, GSK is entitled to the presumption that it is "not liable with respect to the allegations involving failure to provide adequate warnings" for Requip. *See* TEX. CIV. PRAC. & REM. CODE § 82.007(a). Dr. Wells has not invoked any of the statute's narrow exceptions, and so the presumption controls as a matter of law.

CONCLUSION AND PRAYER

For these reasons, Defendant SmithKline Beecham Corporation d/b/a GlaxoSmithKline requests that the Court grant summary judgment on Dr. Wells' warning claims for failure to warn because they are:

(i) preempted under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 *et seq.*) or alternatively,

(ii) barred under Texas Civil Practice and Remedies Code § 82.007 because: (a) GSK has established that on the uncontrovertible record that its warnings have been at all times approved by FDA; and (b) Dr. Wells has not pled any exception or factual basis for overcoming the presumption.

Dated: July 21, 2008

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on the 21st day of July, 2008, I electronically filed the foregoing with the Clerk of Court using the CM/ECF system, which will send notification of such filing to the following:

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